Amendments to the Drawings:

Applicants submit herewith replacement sheets of drawings for Figures 1-3. These replacement sheets of Figures have been amended to include a recitation of the "SEQ ID NO" corresponding to each of the nucleotide and/or amino acid sequences in the sequence listing that are present in said Figures. Applicants submit that no new matter is introduced into the specification by way of the replacement sheets of Figures.

REMARKS

Amendments to the Claims

Reconsideration of this application is respectfully requested. Upon entry of the foregoing amendment, claims 15-37 remain pending in the application. Claims 16-25 and 28-34 are currently amended. Claims 35-37 are newly added.

Applicants respectfully request entry of the above amendment and submit that the above amendment does not constitute new matter. Support for amended claims 16-25 and 28-34 and new claims 35-37 can be found throughout the specification and in the claims as originally filed. Support for the amendments to claims 16-19 and 32-34 can be found, for example, at paragraphs [20]-[24] and [68]-[69] of the specification and in the claims as originally filed. Support for the amendments to claim 20 can be found, for example, at paragraphs [14] and [23] of the specification. Support for the amendments to claim 21 can be found, for example, at paragraphs [44] and [45] of the specification. Support for the amendments to claims 22 and 24 can be found, for example, at paragraphs [44] and [46] of the specification. Support for the amendments to claims 23 and 25 can be found, for example, at paragraph [44] of the specification. Support for the amendments to claims 28-31 can be found, for example, at paragraphs [19] and [53] of the specification. Support for new claims 35-37 can be found, for example, at paragraph [43] of the specification, Figures 1-3 and in the claims as originally filed.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Substitute Sequence Listing

In reply to the Office Action, and in accordance with the provisions of 37 C.F.R. §§ 1.821-1.825, Applicants submit herewith a computer readable form (CRF) of the substitute "Sequence Listing" on a 3½ inch diskette, in ASCII format as required by 37 C.F.R. § 1.821(e). Applicants also submit herewith a paper copy of the substitute "Sequence Listing," totaling four (4) pages. Applicants have also amended Figures 1-3 and page 29 of the specification to include SEQ ID Numbers.

Support for the substitute sequence listing can be found throughout the specification as originally filed, *inter alia*, on pages 29 and 30, Figures 1-3 and the original sequence listing as

filed. Applicants submit that no new matter is introduced into the specification by way of incorporation of the instant substitute sequence listing. Applicants respectfully request entry of this sequence listing into the specification.

The undersigned hereby states on information and belief that the content of the computer readable form of the substitute "Sequence Listing" and the paper copy of the substitute "Sequence Listing" submitted herewith are the same.

Information Disclosure Statement

The Office Action states that the Information Disclosure Statement filed on March 10, 2004 fails to comply with 37 C.F.R. § 1.98(a)(3) because it does not include a concise statement of relevance for certain references that are in Japanese. Specifically, the Examiner states that JP 08510998T2, Igaku, J. March 1994, Igaku, J. May 1994 and Moriyama et al. 1999 are in Japanese do not have a concise statement of their relevance in English.

Applicants submit the following as a concise explanation for JP 08510998T2, Igaku, J. March 1994, Igaku, J. May 1994 and Moriyama et al. 1999:

JP 08510998T2, proposes a method that is intended to treat certain kinds of disease either through the function of actin binding proteins (ABPs) or by regulating the ABP function, i.e., a method for treatment or disease alleviation by administering ABP to morbid tissues or organs resulting from actin deposits. *See* paragraph [12] of the specification.

Igaku, J. (March 1994), describes that patients with lethal hereditary diseases, certain malignant tumors and AIDS, which currently have no effective methods of treatment, are being subjected to trials of gene therapy for complementing deficient or mutated genes. *See* paragraph [5] of the specification.

Igaku, J. (May 1994), describes that Cofilin is a protein having molecular weight of about 19,000 and a member of actin-binding proteins (ABP) that bind to actin filaments (F-actin) at a molar ratio of 1:1 in response to a variety of signals, thus regulating the physical conditions of actin and performing primary function in the reconstitution of the actin-based cytoskeleton. *See* paragraph [10] of the specification.

Moriyama et al. (1999), describes that Cofilin, by binding to G-actin and cutting G-actin (actin monomer) and depolymerizing it, controls many cell responses including changes in

shape, movements (motion), division, secretion, phagocytic (pinocytic) action, various signal transductions, etc. *See* paragraph [10] of the specification.

In view of the above, Applicants respectfully request that the Examiner consider the Information Disclosure Statement filed on March 10, 2004, by initialing next to JP 08510998T2, Igaku, J. March 1994, Igaku, J. May 1994 and Moriyama et al. 1999, on the PTO/SB/08A (modified) in accordance with M.P.E.P. § 609.

Objections to the Specification

The Office Action objects to the specification because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have amended the specification to delete the embedded hyperlink.

The Office Action also objects to the specification because the title of the invention is allegedly not descriptive. Applicants have amended the title to recite, "Methods of Promoting the Growth or Differentiation of Hematopoietic Stem or Progenitor Cells By Non-Muscle Type Cofilin."

In view of these amendments, Applicants respectfully request the withdrawal of the objections to the specification.

Claim Objections

The Office Action objects to claims 16-17, 21-25 and 32 because they are missing a word in the phrase "growth, differentiation or hematopoietic stem cells...". Applicants have amended claims 16-17, 21-25 and 32 by reciting, "growth or differentiation of hematopoietic stem cells...". Accordingly, Applicants respectfully submit that the above amendment obviates the objection to the claims.

Rejections under 35 U.S.C. § 101

The Office Action states that claims 19-20 and 34 are rejected under 35 U.S.C. § 101 because the claims allegedly recite a use without setting forth any steps involved in the process. Applicants have amended claims 19-20 and 34 to recite the step of "administering." Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 101.

Rejections under 35 U.S.C. § 112, 1st paragraph

A. Enablement

The Office Action states that claims 16-34 are rejected under 35 U.S.C. § 112, 1st paragraph, because the specification, (while being enabling for (1) a method of promoting the growth of hematopoietic stem cells and hematopoietic progenitor cells *in vitro* or *ex vivo* comprising administering human non-muscle type Cofilin of SEQ ID NO: 1 to hematopoietic stem cells or hematopoietic progenitor cells *in vitro* or *ex vivo* to promote growth and (2) a method of promoting the differentiation of hematopoietic stem cells and hematopoietic progenitor cells *in vitro* or *ex vivo* comprising administering human non-muscle type Cofilin of SEQ ID NO: 1 and one or more cytokines to hematopoietic stem cells and hematopoietic progenitor cells *in vitro* or *ex vivo* to promote differentiation), does not reasonably provide enablement for a method of treating a disease or promoting growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells said method comprising administering at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter contains Cofilin as an active ingredient. The Office Action also alleges that the specification does not reasonably provide enablement for a method of regenerative medicine or expanding hematopoietic stem cells *ex vivo* by using at least one promoter of growth, differentiation of hematopoietic stem cells, hematopoietic progenitor cells, wherein said at least one promoter includes Cofilin as an active ingredient. (*See* page 5 of the Office Action).

Applicants respectfully traverse the rejection and provide the following remarks.

Applicants have discovered that Cofilin promotes the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitor cells. In particular, the inventors found that Cofilin promotes HPP-CFC (high proliferative potential-colony cell) expansion, thereby demonstrating that Cofilin promotes the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitor cells. (*See e.g.*, Example 3, Figure 4 and paragraphs [28], [36] and [38]).

Cofilin proteins are known in the art to constitute a family of actin-binding proteins. Indeed, as the Office action points out, "[r]elevant literature teaches that there are at least twelve known mammalian Cofilins.". (*See* page 8 of the Office Action). Cofilins are low molecular weight proteins (15-21 kDa) that occur universally in eukaryotes. Cofilin in every higher

vertebrate animal each consist of 166 amino acids. Accordingly, Cofilin proteins are well known in the art and have been well characterized in the literature.

The claimed invention is drawn to methods that require the administration of at least one promoter that has the activity of Cofilin of promoting growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. Thus, the claimed methods are limited to administering only those Cofilin proteins that have the activity of promoting growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors.

The specification teaches that the activity of the Cofilin in promoting the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors may be determined with reference to the activity in promoting the expansion of HPP-CFCs. (*See* paragraphs [36] and [37], for example). For instance, in Example 3, Applicants disclose a non-limiting example demonstrating that one type of Cofilin, human non-muscle type Cofilin, promotes HPP-CFC expansion and thus has HPP-CFC activity. (*See e.g.*, paragraphs [107]-[108]). By inducing the HPP-CFC expansion, human non-muscle type Cofilin demonstrated that it promotes the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. Accordingly, one of skill in the art may determine whether a particular Cofilin protein has the activity of promoting growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors using routine experimentation disclosed in the specification.

The Office Action purports that the specification does not teach the administration of any Cofilin to any subject for the promotion of growth and differentiation of hematopoietic stem cells or progenitor cells. The Office Actions further purports that the specification does not teach the treatment of any diseases that result from insufficient growth or differentiation of hematopoietic stem cells or hematopoietic progenitors comprising the administration of Cofilin. In addition, the Office Action purports that a large quantity of experimentation would be required by one skilled in the art to treat all possible diseases that result from insufficient growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. (*See* page 7 of the Office Action).

Applicants respectfully traverse.

As discussed in the "Background of the Invention," Applicants describe previous methods of treating diseases that result from insufficient growth or differentiation of hematopoietic stem cells or hematopoietic progenitors. In particular, previous methods showed

that agents that promote the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors are useful in treating diseases associated with hematopoietic hypofunction caused by anti-cancer agents, radiation etc. In the instant case, Applicants have shown that Cofilin promotes the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors.

Applicants respectfully submit that since Cofilin is shown to promote the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors, one of ordinary skill in the art armed with applicants' specification would readily appreciate that Cofilin may be used in treating diseases that result from insufficient growth or differentiation of hematopoietic stem cells or hematopoietic progenitor cells. Applicants also submit that those of ordinary skill in the art can easily determine the route of administration, as well as the appropriate dose and/or dosing period. Accordingly, Applicants submit that an undue quantity of experimentation would not be required by one skilled in the art to carry out the invention as claimed.

The Office Action purports that the specification does not teach that human non-muscle type Cofilin *alone* is able to promote the differentiation of hematopoietic stem cells or hematopoietic progenitor cells.

Applicants again respectfully traverse.

It is known in the art that HPP-CFC proliferate and differentiate simultaneously. In particular:

> Colony-forming cells with a high proliferative potential (HPP-CFC) have been defined by their ability to form large colonies in vitro (diameters greater than 0.5 mm and containing approximately 50,000 cells) in bone marrow cell cultures. The HPP-CFC have been characterized by: 1) a relative resistance to treatment in vivo with the cytotoxic drug 5-fluorouracil, 2) a high correlation with cells capable of repopulating the bone marrow of lethally irradiated mice, 3) their multipotential ability to generate cells of the macrophage, granulocyte, megakaryocyte and erythroid lineages, and 4) their multifactor responsiveness. The HPP-CFC have been described in both mouse and human bone marrow. These properties suggest that the HPP-CFC represent an important cell type in hematopoiesis and provide a model system, particularly in the human, for studying the properties of primitive progenitor cells in vitro. *See* Int J Cell Cloning 8:146-160 (1990).

The specification teaches that the administration of human non-muscle type Cofilin *alone* promotes the expansion of HPP-CFC. (*See e.g.*, Fig. 4 and paragraphs [107] and [108]). Accordingly, by demonstrating that the administration of human non-muscle type Cofilin *alone*

induces HPP-CFC to proliferate, Applicants submit human non-muscle type Cofilin *alone* is able to promote the differentiation of hematopoietic stem cells or hematopoietic progenitor cells.

In view of the above arguments, Applicants respectfully request withdrawal of the enablement rejection.

B. Written Description

The Office Action states that claims 16-34 are rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement.

The Office Action purports that specification does not provide adequate written description of the clamed genus because the specification does not provide sufficient distinguishing identifying characteristics, such as complete or partial structure, functional characteristics and methods of making the claimed product. The Office Action purports that the disclosure of one species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments with at least 30% sequence identity to the polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The Office Action concludes by stating that only a human non-muscle type Cofilin comprising the amino acid sequence of SEQ ID NO: 1 or a human non-muscle type Cofilin encoded by the base sequence of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. (*See* page 15 of the Office Action).

Applicant respectfully disagrees and traverses this rejection.

At the outset, it is noted that the claims are not drawn to Cofilin proteins *per se* but rather are drawn to methods that require the administration of at least one promoter that has the activity of Cofilin and further that promotes growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. Accordingly, the claimed methods are limited to administering only those Cofilin proteins that have the activity of promoting growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors.

Thus, the present application claiming a novel and unobvious method employing a known set of proteins should in no way be confused with those instances where the point of novelty rests in the structure of a new biological molecule, whereby a distinguishing description is necessary for compliance with the written description requirement. The fact of the matter is that Cofilin proteins are known in the art to constitute a family of actin-binding proteins. Indeed,

as the Office action points out, "[r]elevant literature teaches that there are at least twelve known mammalian Cofilins.". (*See* page 8 of the Office Action). Cofilins are low molecular weight proteins (15-21 kDa) that occur universally in eukaryotes. Cofilin in every higher vertebrate animal each consist of 166 amino acids. Accordingly, Cofilin proteins are well known in the art and have been well characterized in the literature.

Recently, in *Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005), the Federal Circuit faced a similar written description issue involving an applicant who claimed a chimeric gene comprised of two known genes. The Board found the written description to be lacking for the claimed chimeric genes "because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results." *Capon, ID* at 1082. In reversing the Board, the Federal Circuit held that:

> The "written description requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh....Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result. *Capon, ID at* 1084-85

In the present case, applicants do not purport to have invented Cofilins. Furthermore, the specification discloses several Cofilin structures. In particular, Figure 3 shows a comparison between human non-muscle type Cofilin derived from human placenta and from human S6 cells. Applicants should not be required to describe that which is already known.

Applicants disclose that the activity of the Cofilin in promoting the growth and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors may determined with reference to the activity in promoting the expansion of HPP-CFCs. (*See* paragraphs [36] and [37], for example). For instance, in Example 3, Applicants disclose a non-limiting example demonstrating that one type of Cofilin, human non-muscle type Cofilin, promotes HPP-CFC expansion and thus has HPP-CFC activity. (*See e.g.*, paragraphs [107]-[108]). By inducing the HPP-CFC expansion, human non-muscle type Cofilin demonstrated that it promotes the growth

and/or differentiation of hematopoietic stem cells and/or hematopoietic progenitors. Accordingly, the specification provides sufficient functional characteristics of the Cofilin proteins used in the invention.

The Office Action purports that claims 22 and 24 do not comply with the written description requirement because the claims recite hybridization conditions that encompass an infinite number of possible polynucleotides. Applicants have amended claims 22 and 24 recite specific hybridization conditions. Accordingly, Applicants respectfully submit that amended claims 22 and 24 comply with the written description requirement.

For the reasons set forth above, Applicant submits that the specification clearly provides adequate written description to demonstrate that Applicant was in possession of the claimed subject matter at the time of filing of the instant application. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the written description rejection of claims 16-34.

Rejections under 35 U.S.C. § 112, 2nd paragraph

The Office Action states that claims 16-34 are rejected under 35 U.S.C. § 112, 2nd paragraph. Applicants respond to each rejection below.

Claims 16-34 are rejected because the claims allegedly do not have a step that clearly relates to the preamble. Applicants have amended the claims to recite language that relates back to the preamble. For example, Claim 16 has been amended to recite, "and promotes growth or differentiation of hematopoietic stem cells, hematopoietic progenitors, or a combination thereof."

Claims 18 and 32 are rejected because the metes and bounds of the term "combination thereof" allegedly cannot be determined. Applicants have deleted "combination thereof" from claims 18 and 32.

Claims 22 and 24 are rejected because the claims allegedly fail to recite clear hybridization conditions. Applicants have amended the claims to recite hybridization conditions.

Claims 28-31 are rejected because there is allegedly insufficient antecedent basis for the recitation of "another cytokine." Applicants have amended the claims to delete "another." Claim 28, which claims 29-31 depend from, now recites, "a cytokine other than Cofilin."

Claims 19-20 and 34 are rejected because the claims allegedly recite a use without any active, positive steps. Applicants have amended claims 19-20 and 34 to recite the step of "administering."

Claims 20 and 34 are rejected because the term "regenerative medicine" is allegedly indefinite. In particular, the Office Action alleges that "one of skill in the art would not be reasonably apprised of the scope of the invention." (See pages 16 and 17 of the Office Action). Applicants respectfully traverse. Applicants submit that the term "regenerative medicine" is a term that is known and used in the art. For example, in a search of U.S. published patent applications the term "regenerative medicine" is present in 192 published applications. Accordingly, Applicants submit that one of skill in the art would be reasonably apprised of the scope of the invention.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 16-34 under 35 U.S.C. § 112, 2nd paragraph.

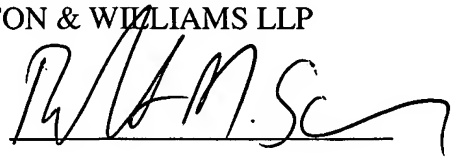
Conclusion

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their undersigned representatives to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: **December 7, 2005**

By: 

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